REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

Claims 1, 9, 11, 12, 19, 21, 30, 34 and 36 are amended herein, to specifically recite HMA and DMA as the claimed agent, as well as to address issues of dependency based on the amendments made herein. New claims 55-66 are added by way of the present Amendment. New claims 55-57 are based on claims 44-49 as-filed; new claims 58-63 are directed to a method of reducing, retarding or otherwise inhibiting the functional activity of HIV where the HIV has infected a mammalian host cell. The method comprises administering to said mammal an effective amount of HMA or DMA for a time and under conditions sufficient to reduce, retard or otherwise inhibit the functional activity of HIV. New claims 64-66 are directed to a method for the treatment and/or prophylaxis of HIV infection or AIDS in a mammal comprising administering an effective amount of HMA or DMA.

Basis for these amendments and new claims may be found throughout the specification and claims as-filed, as the specification throughout discloses that HMA and DMA possess antiviral activity, *i.e.*, that HMA and DMA are in fact anti-viral compounds, regardless of their mechanism of action.

Claims 6, 7, 8, 10, 16, 17, 18, 20, 22-29, 32, 33, 35 and 37-54 are canceled herein without prejudice or disclaimer thereto. Applicants reserve the right to file at least one continuation or divisional directed to any subject matter canceled by way of the present Amendment.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-7, 12-17, 30-32, 37-39, 44, 45, 50-54 stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly failing to comply with the written description requirement. Specifically, the Office Actions states that the phrase "amiloride analogue" can encompass an unlimited number of compounds, and that the specification fails to provide written description as to how to make or use the "amiloride analogue".

In the interest of expediting prosecution, the claims reciting the term "amiloride analogue" have been canceled without prejudice or disclaimer thereto, or amended to remove this phrase. Thus, this rejection is moot.

Claims 1-7, 12-17, 30-32, 37-39, 44, 45, 50-54 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for HMA, DMA or amiloride, purportedly fails to provide enablement for any other compounds which may meet the definition of "amiloride analogue". Claims 1, 12 and 30 are amended herein to recite that an effective amount of "HMA or DMA" is administered to the subject, and the reference to "amiloride analogue" has been removed. Thus, as the amended claims recite subject matter which the Examiner considered enabled, Applicants submit this rejection is obviated.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 22-29 stand rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite, as the claims are purportedly "use" claims which do not recite method steps. Claims 22-29 are canceled herein. Thus, this rejection is moot.

Claim Rejections Under 35 U.S.C. § 101

Claims 22-29 stand rejected under 35 U.S.C. § 101, as purportedly reciting a use without steps involved in the process. As noted above, claims 22-29 are canceled herein. Thus, this rejection is moot.

Claim Rejections 35 U.S.C. § 102

Claims 37-49 stand rejected under 35 U.S.C. § 102(b) as purportedly anticipated by Burke (US 5,215,991). Burke allegedly discloses a pharmaceutical composition comprising N,N-hexamethylene amiloride, or N, N-dimethyl amiloride. First, Applicants note that claims 37-49 are canceled herein without prejudice or disclaimer, and are replaced with new claims 55-57. With regard to new claims 55-57, Applicants traverse.

Applicants submit that Burke fails to recite every element of the presently claimed invention. To anticipate a claim, a single prior art reference must teach each and every element of the claimed invention. *See* M.P.E.P. 2131; *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); *Hybritech Inc.v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986).

New claims 55-57 are directed to an antiviral pharmaceutical composition comprising an effective amount DMA or HMA and/or more pharmaceutically acceptable carrier and/or diluent, wherein the composition has an antiviral effect. Burke does not disclose an antiviral effect. Thus, the cited reference does not recite all of the elements of the present invention. Applicants request that the rejection be withdrawn.

Claim Rejections 35 U.S.C. § 103

Claims 1-21, 30-36 and 50-54 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Lipton (US 5,506,231), in view of Benos et al. and Burke (US 5,215,991). Lipton purportedly discloses a method for treating a patient infected with HIV, comprising administering an effective amount of Ca+ ion channel antagonist. However, Lipton does not disclose the use of amiloride for treating an HIV infected patient. The Office Action states that it would have been obvious to the skilled artisan to use amiloride, or its analog, as Ca+ channel antagonist for treating HIV infected patients. Applicants traverse.

In order to establish a case of *prima facie* obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference or combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art reference(s) must teach or suggest all of the claim limitations. *See* M.P.E.P. 2142. Applicants respectfully submit that these criteria have not been met in the present Office Action.

The cited references, alone or in combination, fail to recite all of the elements of the presently claimed invention or to provide an expectation of success or motivation to arrive at the claimed invention.

Lipton, the primary reference, discloses the treatment of central nervous system disorders caused by infection with HIV. Specifically, Lipton discloses methods of reducing damage to CNS neurons, and reducing HIV-related vision loss, myelopathy or dementia in human patients infected with HIV, by administering a therapeutic composition. This composition is an antagonist of the NMDA receptor-

channel complex, capable of reducing the gp120-responsive rise in free Ca^{2+} ion concentration in the patient's CNS neurons. Amiloride is listed as only one possible antagonist of the NMDA receptor-channel complex. However, as noted by the Examiner, Lipton does not disclose the use of an antagonist of Ca^{2+} channels for the treatment of HIV infection itself. Instead, Lipton only discloses the reduction of damage to the central nervous system caused by HIV infection.

The secondary references fail to remedy the deficiencies of Lipton even when taken in combination with Lipton. Benos discloses that adding either killed HIV virus or purified gp120 to media bathing rat astrocytes results in changes in activity of a number of plasma-membrane-located ion channels and transporters. The addition of amiloride appears to inhibit the perceived changes in ion channel and transporter activity. However, Benos does not teach or suggest the use of amiloride to inhibit the Vpu ion channel of HIV or treatment.

Burke discloses that combinations of $alpha_2$adrenoreceptor agonists and Na+/H+ exchange inhibitors are useful in lowering intraocular pressure. Thus, Burke discloses a method for lowering intraocular pressure comprising co-administrating to the eye of a mammal suffering from ocular hypertension an $alpha_2$agonist and a potentiating amount of a Na+/H+ exchange inhibitor. Burke discloses the use of amiloride, HMA and DMA as preferred by Na+/H+ exchange inhibitors. However, Burke does not remedy the deficiencies of the other references because Burke provide no teaching or suggestion of treatment HIV, or that HMA or DMA block Vpu ion channels of HIV or inhibit functional activity of HIV. Therefore, Burke does not disclose that HMA or DMA are useful in treating an HIV infected patient.

Taken in combination, the cited references fail to satisfy a *prima facie* case of obviousness. The Office Action argues that the skilled artisan would have been motivated to use amiloride or an analog thereof, such as HMA or DMA, as a CA^{2+} channel antagonist for treating HIV infected patients, because amiloride is purportedly known to negate the toxic effect introduced by HIV toxic protein, and the amiloride analogues HMA and DMA are known to be similarly useful as amiloride. Applicants respectfully disagree.

The Office Action cites Benos as reciting amiloride as a treatment for cells infected with HIV. Applicants emphasize that Benos does not disclose the use of amiloride as a treatment for cells infected with HIV. Instead, Benos merely discloses the effect of amiloride on astrocytes exposed to killed HIV virus or purified gp120 from an external source. Therefore, Applicants note that the astrocytes of Benos are not infected with HIV and do not express HIV proteins. Instead, these astrocytes are merely exposed externally to killed HIV or purified gp120 protein. This external exposure causes changes in the activity of a number of plasma-membrane-located ion channels and transporters, and amiloride appears to inhibit the perceived changes in ion channel and transporter activity of the non-infected cells. Therefore, Benos does not teach or suggest an effect of amiloride on cells infected with HIV and bearing an HIV ion channel protein. Furthermore, Benos does not even teach or suggest that HIV gp120 protein forms ion channels. Instead, it only discloses that added gp120 appears to change the activity of membrane-located ion channels in non-HIV infected cells. Therefore, Benos does not teach or suggest the use of amiloride in the inhibition of an ion channel in a cell infected with HIV.

Applicants note that the specification of the present application discloses that amiloride itself does not inhibit or block the Vpu ion channel of HIV. Applicants refer the Examiner to the present specification at page 14, lines 3 to 9, reciting that the structure of amiloride is incompatible with the structure of the HIV Vpu ion channel. In fact, Benos teaches away from the present invention in this respect, because Benos describes the use of amiloride in blocking ion channel effects. Moreover, Benos does not teach or suggest the use of amiloride in blocking HIV replication. Because Benos fails to disclose or suggest amiloride in the context of HIV-infected cells, Benos does not teach or suggest the use of amiloride in blocking HIV replication.

The present invention teaches that amiloride does not inhibit the HIV Vpu ion channel. Therefore, HMA and DMA would not be expected by the skilled artisan to inhibit the HIV Vpu ion channel or inhibit HIV functional activity. None of the cited references provide motivation to combine the references to arrive at a composition which inhibits the HIV Vpu ion channel or even inhibit HIV activity.

Lipton, the primary reference, does not disclose or suggest the use of an ion channel antagonist for the treatment of HIV infection. Burke does not disclose or suggest the use of HMA or DMA in treating HIV infection. In light of the above remarks Applicants respectfully submit that the disclosures by Lipton and Burke in combination with disclosures by Benos do not provide a disclosure necessary to motivate the skilled artisan to utilize HMA or DMA to inhibit the HIV Vpu ion channel and to inhibit HIV replication.

In light of the above remarks, Applicants request that the rejection under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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